

REMARKS

In response to the Office Action mailed January 26, 2005, Applicants canceled claims 1-8 and 28-30, and added new claims 31-34. Claims 9-27 and 31-34 are presented for examination.

Drawings

Applicants amended figure 1 to conform with the requirements of 37 CFR § 1.84(u)(1).

Specification/Informalities

Applicants amended the title to address the issue raised by the Examiner.

Claim Objections

Applicants amended claims 12 and 20 to recite "beta-amyloid precursor protein." These amendments are believed to overcome the Examiner's objections.

35 U.S.C. § 112, second paragraph

The Examiner rejected claims 9-27 under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner asserted that claims 9-27 omit essential steps, referencing M.P.E.P. § 2172.01. However, this section of the M.P.E.P. relates to circumstances where an Applicant discloses that certain subject matter is critical. Applicants made no such disclosure in the present application. The Examiner also refers to a portion of the Trilateral Report to support this rejection. However, Applicants believe that this portion of the Trilateral Report does not address 35 U.S.C. § 112, second paragraph.

With respect to claims 12, 15, 20 and 23, Applicants replaced the terms "designing" and "designed" with the terms "identifying" and "identified," respectively. After reading the application as originally filed (*e.g.*, page 10, paragraph 33) one skilled in the art would understand what is meant by these terms.

Regarding claims 16 and 24, after reading the application as originally filed, one skilled in the art would understand what is meant by the phrase noted by the Examiner. For example, pages 11 and 12 (paragraph 35) of the application as originally filed provide guidance in this regard.

As presented, Applicants believe that, regarding claims 12-14, 17, 18 and 20, the issue raised by the Examiner in connection with the phrase "identifying an agent" has been obviated.

Claims 9-27 recite particular coordinates by reference to the figures included in the application as originally filed. Furthermore, in one embodiment, BACE is a protein having the amino acid sequence defined at page 5, paragraph 16 by the sequence of Swiss Prot Accession No. P56817 including conservative substitutions. *See*, SEQ ID NO:1; copy of Swiss Prot Accession No. P56817 GenBank entry enclosed with the accompanying information disclosure statement (IDS). In one embodiment, the term "APP" is defined as a protein having the amino acid sequence defined at page 5, paragraph 16 by the sequence of Swiss Prot Accession No. CAA31830, a fragment of this protein, or a protein having conservative substitutions. *See*, SEQ ID NO:2; copy of Swiss Prot Accession No. CAA31830 GenBank entry enclosed with the accompanying IDS. Accordingly, upon reading the application as originally filed, one skilled in the art would clearly understand what is meant by the terms "BACE," "APP binding protein or peptide" and "APP" as they appear in the claims.

With respect to claims 16, 19, 24, and 27, Applicants believe that there is no *per se* requirement to limit a method claim to specifically recite whether the methods covered by the claim are performed *in vitro*, *in vivo*, or *in silico*.

In view of the foregoing, Applicants request withdraw of the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, first paragraph (Written description)

Claims 9-27 were rejected under 35 U.S.C. § 112, first paragraph for failing to satisfy the written description requirement.

In making this rejection, the Examiner asserted that:

the genus of recited active sites encompasses species that are widely variant, including active sites of structural coordinates of mutants and homologs of human BACE from any source, including mutants having function other than BACE or no function at all. (Office Action at 9.)

However, contrary to the Examiner's assertion, the claims are explicitly limited both in terms of the polypeptides covered by the claims (*e.g.*, BACE) and by the coordinates of the polypeptides.

The Examiner also asserted that:

The genus of recited agents encompasses agents having any structure, including small organic molecules and peptides that have the ability to bind to proteins other than BACE having the structural coordinates as set forth in Fig. 1. (Office Action at 9.)

The claims, however, are limited to agents that interact with an active site of the polypeptides recited in the claims. The definition of the term "active site" is provided in the application as originally filed at page 7 (paragraph 26). Additional disclosure that provides relevant, identifying characteristics including structural and functional features of active sites is provided in the application as originally filed at, for example, pages 7 and 8 (paragraph 27).

In view of the foregoing, Applicants believe that the written description requirement has been satisfied, and therefore request reconsideration and withdrawal of this rejection.

35 U.S.C. §112, first paragraph (Enablement)

Claims 9-27 were rejected under 35 U.S.C. §112, first paragraph for failing to satisfy the enablement requirement. In *In re Wands* 858 F.3d 731 (Fed. Cir. 1998), the United States Court of Appeals for the Federal Circuit described the factors to be considered and balanced when determining whether a disclosure satisfies the enablement requirement. The Wands factors are discussed below.

The breadth of the claims:

The subject matter covered by the claims is no broader than Applicants' contribution.

The nature of the invention:

The invention generally relates to methods for identifying agents that interact with an active site of an APP-binding polypeptide, such as BACE. The methods include identifying an active site of the polypeptide using the relative structural coordinates of the polypeptide represented in Figures 1A-1EEE, performing computer fitting analysis to identify an agent which interacts with the active site, and obtaining the agent.

The state of the prior art:

No one has previously disclosed or suggested the methods covered by the pending claims.

The level of one of ordinary skill in the art:

In general, one of ordinary skill in the art would likely have an advanced degree in biology (*e.g.*, protein biology) or a related field, and possible additional experience.

The level of predictability in the art:

The relevant art is generally unpredictable. However, the present application discloses sufficient information to allow one of ordinary skill in the art to successfully implement the methods covered by the claims with a reasonable degree of predictability.

Guidance and working examples:

Applicants disclose a working example that describes the determination of the three-dimensional structure of human BACE1, and the coordinates are provided in Figures 1A-1EEE. *See* Application at page 12 *et seq.* (Example 1). Applicants provide additional guidance throughout the application as originally filed, regarding, for example, active sites and agents which interact with active sites.

The amount of experimentation required:

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, M.P.E.P §2164.01 citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983),

aff'd. sub nom. As discussed above, Applicants have disclosed methods for identifying compounds that bind BACE and APP-binding proteins using an active site defined within the relative structural coordinates of Figures 1A-1EEE. The crystal structure of BACE bound to an inhibitor peptide is described in the specification at pages 16-19, paragraphs 47-57. The claimed methods are described at pages 10-12, paragraphs 33-35. Accordingly, the quantity of experimentation needed to make and use the invention is not undue.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph.

35 U.S.C. §§ 102(a)/103(a)

Claims 9-15, 17-18, 20-23, and 25-26 were rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Sauder *et al.* (*J. Mol. Biol.* 300:241-248, 2000).

Sauder does not disclose the relative structural coordinates of Figures 1A-1EEE. For example, there are several gaps in the crystal structure coordinates of the Sauder models including at the residues spanning positions 220-229, 319-325, and 345-355. *See, e.g.*, Sauder at figures 2 and 3 and the structural coordinates referenced at p. 247, col. 1. These gaps do not exist in the structural coordinates of Figures 1A-1EEE. Therefore, Sauder does not anticipate claims 9-15, 17, 18, 20-23, 25 and 26.

Moreover, based on Sauder, one skilled in the art would not have had a reasonable expectation of success of obtaining the coordinates of Figures 1A-1EEE. As known to those skilled in the art, generating a protein crystal is not a trivial task.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 9-15, 17-18, 20-23, and 25-26 under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Sauder.

Claims 9-27 were rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Tang *et al.* (U.S. Patent 6,545,127).

Tang does not disclose the structural coordinates of Figures 1A-1EEE. For example, the BACE residues included in the Tang crystal (amino acids Ala14 to Thr454) are different than the residues included in Figures 1A-1EEE (amino acids Thr47 to Tyr460 plus nine extra residues due to a cloning artifact) (numbering of amino acids is according to Applicants' specification). *See*, Tang, col. 18, lines 31-34 and col. 29, lines 35-39, and Applicants' specification at page 14, par. 41 and page 15, par. 45 (note that in col. 18 of Tang, the numbering of amino acid residues is according to SEQ ID NO:3 of Tang which numbering corresponds to (n - 2) according to the numbering of the BACE sequence in Applicants' specification). Thus, Tang does not anticipate claims 9-27. Furthermore, as with Sauder, Tang would not have provided one skilled in the art with a reasonable expectation of success in obtaining the coordinates of Figures 1A-1EEE.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e) as anticipated by or by 35 U.S.C. § 103(a) as obvious over Tang.

35 U.S.C. § 103(a)

The Examiner rejected claims 9-15, 17-18, 20-23, and 25-26 under 35 U.S.C. § 103(a) as being unpatentable over Balaji in view of *In re Gulack*. As amended, the claims require obtaining an agent. Neither Balaji nor *In re Gulack*, alone or in combination, disclose or suggest such methods. There is no suggestion to combine them to provide such methods, and, even if combined, they would not result in the methods covered by claims 9-15, 17-18, 20-23, and 25-26. Applicants therefore request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Applicants believe the application is in condition for allowance, which action is requested.

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Please apply any necessary charges or credits to Deposit Account No. 06-1050, with reference to Attorney Docket No. 16163-015001.

Respectfully submitted,

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